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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/574,443	Applicant(s) DAHIYAT et al.
	Examiner Christine Saoud	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 10, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17 and 22-29* is/are pending in the application.

4a) Of the above, claim(s) *23-29* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-17 and 22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-17 and 22-29* are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5,9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I (claims 1-17) and the protein of SEQ ID NO:7 in Paper No. 14 is acknowledged. The traversal is on the ground(s) that "the election of species presently imposed makes it difficult, if not impossible, to obtain a claim as broad as claim 1 which is directed to IA proteins that are less than 97% identical to the wild type insulin proteins. Moreover, such an additional restriction requirement is not in keeping with Applicant's invention.". This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). The Examiner has shown that the inventions of Groups I-II are distinct for the reasons in the previous Office action (see paper #12) as well as providing reasons for distinction for the different proteins. Burden of search is established in that each protein, with each different substitution and activity would need to be searched and that prior art for one protein with certain substitutions would not be prior art for a different protein with a different set of substitutions. Therefore, there is a *prima facie* case that the search and examination of the plural inventions would impose a serious burden upon the Examiner. Applicant has offered no evidence to rebut this showing. Applicant further argues that the Examiner has overlooked the underlying computational method upon which the invention is based. This argument is not persuasive because the method is not the claimed invention; the proteins are and the proteins are independent and distinct because no common structural or functional properties are shared (structure is

different because each has different amino acid structure and function is different since the claim requires "altered property"). Applicant is reminded that this was not an election of species (as asserted at page 6 of the response), but an election of invention (see page 3, paragraph 3 of paper #12).

The requirement is still deemed proper and is therefore made FINAL.

2. Newly submitted claims 23-29 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly submitted claims are directed to a method executed by a computer, which is not classified with the protein. Additionally, the method does not make the claimed proteins, but rather predicts amino acid sequences, therefore, the method is not related to the elected protein claims.

Since applicant has elected to receive an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23-29 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Specification

3. The abstract of the disclosure is objected to because it uses the term "novel". This is a comparison with the prior art, which is not permitted. Correction is required. See MPEP § 608.01(b).

Claim Objections

4. Claim 3 is objected to because of the following informalities: embodiment of "B7-Y" is listed twice. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 1-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for proteins which bind the insulin receptor and have an activity of insulin, does not reasonably provide enablement for proteins which bind to a cell which comprises an insulin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are directed to non-naturally occurring proteins which have an activity of insulin, although altered when compared to the same activity of human insulin, wherein the protein binds to a cell comprising an insulin receptor. However, the claims do not require that the non-naturally occurring protein bind to an insulin receptor, only to a cell which comprises an insulin receptor. Therefore, the non-naturally occurring protein could have an activity of insulin (such as a three-dimensional structure or antigenicity) and bind to a cell, but not necessarily to the insulin receptor (not a limitation of the claim). The instant specification fails to teach how to use a protein which has an activity of insulin which is not related to an activity which is mediated by binding the insulin receptor. For example, the claims encompass proteins which are three-dimensionally similar to insulin, but do not bind the receptor but may bind a cell that has the

receptor, and therefore, these proteins would not have an activity mediated by the receptor. There is no disclosure of how these molecules are to be used. Additionally, the instant claims are based on a computer method of determining likely amino acid substitutions which would result in functional proteins with altered biological activity compared to the native protein. However, the final step in mutational analysis is the making and testing of the proteins which are predicted. Without such a determination, it is not predictive which hypothetical proteins will function in a manner which could be used by one of ordinary skill in the art. This is supported by the fact that the claims encompass mutation of position 19 of the A-chain, but Kristensen et al. teach that TyrA19 is essential for binding to the insulin receptor (see page 12978 at column 2, paragraph 4), and therefore, it is unpredictable which amino acids could be substituted at this position and still result in a functional molecule which has insulin activity and binds the insulin receptor. Furthermore, without knowing which property is possessed (or altered) in comparison to the native protein, it is not reasonable for one of ordinary skill in the art to use the protein. For example, if the property which is altered is biological stability, one would need to know if the stability is increased or decreased in order to use the insulin mutant in a real world manner. If the property which is altered is the ability to bind the insulin receptor, then this would need to be known in order to use the mutant in a real world manner. There is no disclosure as to how the various positions and combinations of substitutions at these positions will affect the properties of the insulin molecules which are being generated, compared to native insulin, therefore, one of ordinary skill in the art at the time of the instant invention would not be able to use the claimed proteins in a real world manner without undue experimentation, absent evidence to the contrary.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-6, 8, 11-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Brange et al. (U.S. Pat. No. 5,618,913).

Brange et al. teach a number of different insulin analogues, wherein the analogues are non-naturally occurring insulin molecules which have an activity of insulin. Since they bind the insulin receptor, they would also bind to a cell which comprises the insulin receptor (see claim 1 limitations). Brange et al. further teach substitutions at positions 1, 2, 5, 9, 10, 12, 14, 16-18, 20, and 26-28 of the B-chain and positions 8-10, 13, and 21 of the A-chain (see claim 12 at column 35), meeting the limitations of claim 6. Brange et al. additionally teach that the insulin analogues are prepared using a DNA encoding the analogue, inserting in an expression vector, transferred into a host cell and expressing the product and isolating the analogue (see column 16), meeting the limitations of claims 11-17.

8. Claims 1, 5, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakagawa et al. (J. Biol. Chem. 261(16): 7332-7341, 1986).

Nakagawa et al. teach substitution of position 25 of the B-chain of insulin (see abstract) with an altered insulin-receptor binding property. Pharmaceutical compositions are taught at page

7333, column 2, under "Biological Assays". Nakagawa et al. therefore anticipate the instant claims.

9. Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Mirmira et al. (J. Biol. Chem. 266(3): 1428-1436, 1991).

Mirmira et al. teach substitution of positions 24, 25 and 26 of the B-chain of insulin (see abstract) with an altered receptor binding potency of insulin. Mirmira et al. therefore anticipate the instant claims.

10. Claims 1-2, 5, 6, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Marki et al. (Hoppe-Seylers Xeitschrift fur Physiologische Chemie 360(11): 1619-1632, 1979).

Marki et al. teach modifications of positions 2, 5, 6, 7, 8, and 11 of the A-chain and positions 5, 7, 13, and 16 of the B-chain of insulin (see Table 1 at page 1622) with altered potencies. Pharmaceutical compositions are taught at page 1630 under "Biological activity in vivo". Marki et al. therefore anticipate the instant claims.

11. Claims 1-2, 5, and 11-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kristensen et al. (J. Biol. Chem. 272(20): 12978-12983, 1997).

Kristensen et al. teach modifications of positions 4, 8, 9, 12, 13, 14, 15, 16, 17, 19, and 21 of the A-chain and positions 1, 2, 3, 4, 8, 9, 10, 11, 12, 13, 16, 17, 18, 20, 21, 22 and 26 of the B-chain of insulin (see abstract) with altered receptor binding affinities. Kristensen et al. additionally

teach that the insulin analogues are prepared using a DNA encoding the analogue, inserting in an expression vector, transferred into a host cell and expressing the product and isolating the analogue (see page 12978, column 2 under "Vector Construction and Expression in Yeast"), meeting the limitations of claims 11-16. Kristensen et al. therefore anticipate the instant claims.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Thursday from 8AM to 2PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud